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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,993	07/13/2001	Lars Nilsson	PH114205.2001/KMZ15101.02	2242

7590 10/01/2003

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EXAMINER

SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
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1636

17

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/903,993	NILSSON ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 July 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 12-22 and 24-46 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 18, 19 and 22 is/are allowed.
- 6) ☒ Claim(s) 1-10, 12-17, 19-21 and 24-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>12</u> . | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

This Office Action is a reply to the "Amendment under 37 C.F.R. 1.111" (Paper No. 13) and Declaration under 37 C.F.R. 1.131 (Paper No. 14) filed 15 July 2003 (Paper No. 13) in response to the Non-Final Office Action mailed 11 February 2003 (Paper No. 11). Claims 1-10, 12-22 and 24-28 were considered, and claims 11 and 23 were withdrawn from consideration in Paper No. 11. Claims 1-9, 13, 14, 17, 19-22 and 24-28 were amended, claims 11 and 23 were canceled, and claims 29-44 were added in Paper No. 13. Claims 1-10, 12-22 and 24-46 are pending and under consideration.

With regard to Applicant's request for clarification as to the status of claims 18, 19 and 22, no grounds for rejection were set forth in the previous Office Action. Therefore, the indication of those claims as rejected on the Office Action Summary was a typographical error.

Oath/Declaration

Objection to the declaration as defective is withdrawn.

Response to Amendment

Drawings

The formal drawings submitted 15 July 2003 are approved by the draftsman.

Specification

Objection to the specification is withdrawn.

Claim Rejections - 35 USC § 112

Claims 1-10, 12-17 and 24-28 stand rejected and newly added claims 29-43 and 46 are rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for the claimed subject matter for reasons of record in Paper No. 11 and herein below in the response to arguments. Claims 29-43 and 46 are rejected insofar as the claims encompass subject matter that was indicated to lack adequate written description in the previous Office Action.

Claims 1-10, 12-17 and 24-28 stand rejected and newly added claims 29-46 are rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter for reasons of record in Paper No. 11 and herein below in the response to arguments. Claims 29-46 are rejected insofar as the claims encompass subject matter indicated in the previous Office Action to lack an enabling disclosure.

Rejection of claims 7, 24 and 25-28 under 35 U.S.C. 112, second paragraph, as indefinite is withdrawn.

Claim Rejections - 35 USC § 102

Rejection of claims 1-3, 5, 6 and 8 under 35 U.S.C. 102(a) as being anticipated by Mucke *et al.* (1999) *Soc. Neurosci. Abstr.* 25:302 is withdrawn in view of the showings in the Declaration.

Claims 1, 5, 6 and 8 stand rejected and newly added claims 29, 31, 35, 36 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Yeung *et al.* (1994) *J. Cell. Biochem. Suppl.* 0:164 or Kuljis *et al.* (1993) *Soc. Neurosci. Abstr.* 19: 1035 for reasons of record and herein below in the response to arguments.

Claims 20 and 21 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kobayashi *et al.* (1994) *Neurosci. Lett.* 172:147-150 for reasons of record and herein below in the response to arguments.

Claims 24-26 stand rejected under 35 U.S.C. 102(b) as being anticipated by Snow *et al.* (1997) WO 97/46664 as evidenced by Anger *et al.* (1991) *Neurotoxicol.* 12:403-413 for reasons of record and herein below in the response to arguments.

Claim Rejections - 35 USC § 103

Claims 1, 7, 10, 12, 13 and 15-17 stand rejected and newly added claims 29 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Yeung *et al.* (*supra*) or Kuljis *et al.* (*supra*) in view of Snow *et al.* (*supra*) for reasons of record and herein below in the response to arguments.

Response to Arguments

Claims 1-10, 12-17, 24-43 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

For reasons set forth in the previous Office Action, only the described transgenic animals, and methods of using said transgenic animals, comprising the wild-type human alpha-1-antichymotrypsin transgene under the transcriptional control of the GFAP promoter or comprising the wild-type human alpha-1-antichymotrypsin transgene under the transcriptional control of the GFAP promoter and the PDGF-hAPP(V717F) with or without a functional endogenous ApoE gene, or the method of measuring the cognitive function in a transgenic mouse wherein the activity of said compound is not limited or limited to an anti-inflammatory agent meet the written description provision of 35 U.S.C. §112, first paragraph.

In response to the rejection of record, Applicant points out that the claims have been amended to recite that the protease inhibitor interacts with amyloid beta-peptides within the brain tissue of a transgenic mouse. Applicant states, "the claims require that the expression product of the protease inhibitor gene has the recited biological function". This argument has been fully considered but is not found persuasive because the specification fails to provide adequate written description for protease inhibitors having the recited biological function. The specification provides a single example of a protease inhibitor having the recited function but provides no description of the structural determinants that are common to protease inhibitors that interact with amyloid beta-peptides within the brain tissue of a transgenic mouse. Thus, the description of the protease inhibitor, a critical element of the claimed subject matter, amounts to a mere recitation of function. An adequate written description of a protein requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what

is required is a description of the protein itself. It is not sufficient to define protein solely by its principal biological property (i.e., it is a protease inhibitor that interacts with amyloid beta-peptides within the brain tissue of a transgenic mouse) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any protein with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a transgenic mouse comprising all proteins that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific amino acid sequences, which provide the means for practicing the invention.

In response to the Examiner's assertion that the phenotype of a transgenic mouse comprising a transgene encoding a protease inhibitor that is not expressed in neuronal cells will have little or nothing in common with the mice reduced to practice, Applicant argues that the promoter used for the ACT experiments in the examples was a GFAP promoter capable of astrocyte specific expression. This argument does not address the Examiner's assertion, however, to the extent that claims are not limited to astrocyte specific expression or to expression by a GFAP promoter. Instead, the broad claims require only that the protease inhibitor is expressed in "brain tissue". Furthermore, as pointed out in the paragraph bridging pages 6-7, there is nothing

to suggest that even limited embodiments of the claimed invention directed to specific protease inhibitors would have the same phenotype as the mouse reduced to practice.

Applicant additionally argues that the skilled artisan would appreciate that other promoters for expression of protease inhibitors in brain tissue could be utilized and provides several examples of such promoters. This argument is not found persuasive, first, because applicant has not described the phenotype of a mouse wherein a protease inhibitor is expressed in brain tissue other than astrocytes and, second, because many of the rejected claims are not limited to any particular promoter.

With regard to written description of compounds having the activity of an inhibitor of an interaction between A-beta peptide and antichymotrypsin, an inhibitor of an interaction between A-beta peptide and apolipoprotein E, an inhibitor of antichymotrypsin expression, an inhibitor of apolipoprotein E expression, an inhibitor of APP expression, or an inhibitor of expression of an A-beta peptide, Applicant submits that such compounds are art recognized and well known to those of ordinary skill. With regard to inhibitors of the interaction between amyloid beta-peptide and antichymotrypsin, Applicant cites peptides composed of all or part of amino acid 1-15 of the A beta-peptide, and peptidomimetics related to this sequence or small molecules designed to mimic the sequence. Applicant further states, "any compound that interferes with the active inhibitory site of antichymotrypsin, such as a protease-related peptide, or small molecule that effectively mimics that peptide, will prevent antichymotrypsin from binding to beta-peptide" (page 14). Applicant similarly argues that peptides corresponding to the sequence between amino acids 12 and 28 of A beta-peptide would inhibit the interaction of apolipoprotein E with A beta beta-peptide. These arguments are not persuasive because, other than the interacting fragments of

A beta-peptide, the description of the broad genus of inhibitory molecules is solely a recitation of function (i.e., mimetics or any compounds that interfere with the active inhibitory site of antichymotrypsin). Applicant additionally cites U.S. Patent Nos. 6,214,569; 5,780,587; and 5,338,663 as examples of descriptions of inhibitors of the interaction between amyloid beta-peptide and antichymotrypsin. However, the cited art is primarily focused on methods of identifying inhibitors of this interaction and provide only limited examples of compounds that actually have the recited activity. Applicant is again reminded that the description of a molecule requires more than a recitation of function or a method for isolating that molecule, what is required is a description of the molecule itself.

Thus, for reasons of record and herein above, claims 1-17 and 24-43 and 46 are rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for the full scope of the claimed subject matter.

Claims 1-10, 12-17 and 24-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse, or methods of using said transgenic mouse, whose genome comprises a transgene comprising a DNA sequence encoding a normal alpha-1-antichymotrypsin operably linked to a GFAP promoter, wherein the mouse might further comprise a second transgene encoding the hAPP(V717F) protein and/or a homozygous knockout of the endogenous ApoE gene and wherein said mice have a phenotype of exacerbated β -amyloidosis, cognitive impairment as measured by radial arm water maze, and hyperphosphorylation of tau, does not reasonably provide enablement for mice comprising transgenes encoding protease inhibitors other than alpha-1-antitrypsin, additional transgenes

other than hAPP(V717F) or knockouts other than ApoE, or for transgenic mice wherein expression of the ACT gene produces symptoms other than those recited in the application. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant's arguments in response to the enablement rejection of record are the same as the response to the written description rejection and are addressed above as they pertain to written description. With regard to enablement, limitation of the claims to a recitation that the protease inhibitor interacts with amyloid beta-peptides within the brain of a transgenic mouse does not overcome the rejection because, for reasons of record, the limitation does not address the unpredictability of phenotype arising from genotype. Claims further limited to a genotype in the absence of an established correlation of the genotype to a phenotype that the skilled artisan would be able to use without first engaging in undue experimentation are not enabled over full scope of the claimed subject matter. Likewise, further limiting the claims to a recitation that expression of the protease inhibitor gene increases the rate or extent of amyloid formation in the brain tissue of the transgenic mouse does not reduce the scope of the claims to what is enabled by the specification. Given the unpredictability of phenotype arising from any given genotype established in the previous office action, claims that encompass transgenic mice comprising widely divergent genotypes are not enabled by simply reciting a desired phenotype, because the skilled artisan would not be able to make the animals encompassed by the claims without having to engage in random trial and error experimentation to make and test each one. Furthermore, as pointed out in the previous Office Action, teachings in the specification indicate that it is very

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likely that few, if any, of the claimed mice would have an Alzheimer's-like phenotype (Paper No. 11, page 13), which is the only phenotype that the specification has taught the skilled artisan how to use. The previous Office Action additionally points out on page 13, "[w]ith regard to making mice having amyloidogenic disease-like phenotypes other than Alzheimer's disease, the specification is silent with regard to how this might be accomplished using any protease inhibitor gene alone or in combination with other genetic manipulations. The specification does not teach any phenotypic characteristics in the mice reduced to practice that would be associated with amyloidogenic diseases other than Alzheimer's disease, and does not suggest that other protease inhibitors might be associated with other types of amyloidogenic diseases." The amendment does not fully address these grounds for the finding of nonenablement.

Thus, for reasons of record and herein above, claims 1-17 and 24-43 and 46 are rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

Claim Rejections - 35 USC § 102

Claims 1, 5, 6 and 8 stand rejected and newly added claims 29, 31, 35, 36 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Yeung *et al.* (1994) *J. Cell. Biochem. Suppl.* 0:164 or Kuljis *et al.* (1993) *Soc. Neurosci. Abstr.* 19: 1035 for reasons of record and herein below in the response to arguments.

Yeung *et al.* and Kuljis *et al.* each teach a transgenic mouse comprising a transgene encoding a normal protease operably linked to a promoter effective for expression of said transgene in the brain tissue of said mouse according to claims 1, 29 and 31. The transgenic

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mouse of either of Yeung *et al.* and Kuljis *et al.* comprise a human antichymotrypsin transgene according to claims 5, 6 and 35, and a phenotype associated with expression of the expression of the antichymotrypsin transgene that is essentially similar to human Alzheimer's disease according to claims 8 and 36. In addition, Yeung *et al.* and Kuljis *et al.* teach lines of transgenic mice, which the skilled artisan would understand comprise progeny comprising homozygous or heterozygous alleles of the transgene according to claim 38. The transgenic mouse taught by Yeung *et al.* and Kuljis *et al.* is the same as the mouse taught in the instant application; therefore, the limitations of the claims are taught by Yeung *et al.* and Kuljis *et al.*

In response to the rejection, Applicant argues that the claims are not anticipated by the art because the Yeung *et al.* and Kuljis *et al.* publications do not provide an enabling disclosure. Applicant concedes that the art discloses transgenic mice carrying an $\alpha 1$ -antichymotrypsin transgene, but argues that the art does not provide any information concerning the genetic constructs used to produce the transgenic animals beyond identification of antichymotrypsin as the transgene. This argument has been fully considered but is not found persuasive because, in order to anticipate the claims, the art need only disclose the claimed invention. The art discloses a transgenic mouse whose genome comprises a transgene comprising a protease inhibitor linked to a promoter effective for expression of said nucleic acid in the brain tissue of said mouse (see Yeung *et al.*, line 19 and Kuljis *et al.* line 10-12), wherein the protease inhibitor (i.e., antichymotrypsin) is normal and interacts with amyloid beta-peptides within the brain tissue of said transgenic mouse. Thus, the art teaches all of the limitations of the rejected claims. Although, as Applicant points out, the art does not disclose the genetic constructs used to make the animals, the claims are not limited to any particular construct. Applicant further argues that

the art does not disclose whether the transgene was expressed in neurons or glia; however, the rejected claims are not limited to expression of a transgene in neurons or glia. Thus, for reasons of record and herein above, the claims are anticipated by the art.

Claims 20 and 21 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kobayashi *et al.* (1994) *Neurosci. Lett.* 172:147-150 for reasons of record and herein below in the response to arguments.

In response to the rejection of record, Applicant has amended the claims such that they recite the additional step of determining whether the compound promotes or inhibits the activity of the protease inhibitor to promote or inhibit cell death. Applicant argues that Kobayashi *et al.* could not be used to determine whether a compound promotes or inhibits the activity of the protease inhibitor because Kobayashi *et al.* treated cultures with β_{25-40} in the absence or presence of antichymotrypsin while a method of determining whether the compound promotes or inhibits the activity of ACT would require treating with ACT in the absence or presence of the compound. This argument has been fully considered but is not found persuasive because Kobayashi *et al.* does in fact treat cultures with ACT alone and with ACT in the presence of β_{25-40} . In figure 1B, Kobayashi *et al.* demonstrates that ACT alone significantly reduces the number of surviving neurons. Further, Kobayashi *et al.* demonstrate in Figure 3B that cell viability in the presence of both ACT and β_{25-40} is still reduced (compare the first open bar to the final closed bar). Given these data, the skilled artisan would know, at least, that β_{25-40} does not inhibit the activity of ACT to inhibit cell death or division. Thus, the ability of a compound to inhibit the activity of a protease inhibitor to inhibit cell death or division is determined by the method of

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Kobayashi *et al.* Therefore, the instant claimed method is anticipated by the teachings of Kobayashi *et al.*

Claims 24-26 stand rejected under 35 U.S.C. 102(b) as being anticipated by Snow *et al.* (1997) WO 97/46664 as evidenced by Anger *et al.* (1991) *Neurotoxicol.* 12:403-413 for reasons of record and herein below in the response to arguments.

In response to the rejection of record, Applicant argues that Snow *et al.* does not teach or suggest the use of a radial arm water maze having an escape platform capable of relocation among the radial arms of the maze. Applicant argues that the Anger *et al.* publication merely cites other publications as indicating the Morris Water Maze and radial arm maze can be used to evaluate learning and memory. This argument has been fully considered but is not found persuasive because, as pointed out in the previous Office Action, Snow *et al.* teaches that the method comprises measuring the effect on behavior in said mouse utilizing standard memory tests known to those skilled in the art, which Anger *et al.* teaches encompasses the radial arm water maze (see Paper No. 11, page 17). Thus, the teachings of Snow *et al.* anticipate the claims as evidenced by the teachings of Anger *et al.*

Claim Rejections - 35 USC § 103

Claims 1, 7, 10, 12, 13 and 15-17 stand rejected and newly added claims 29 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Yeung *et al.* (*supra*) or Kuljis *et al.* (*supra*) in view of Snow *et al.* (*supra*) for reasons of record and herein below in the response to arguments.

In response to the rejection of record, Applicant argues that the claimed invention is not obvious over the teachings of the cited art because Yeung *et al.* (*supra*) or Kuljis *et al.* do not provide an enabling disclosure of the claimed invention. However, for reasons set forth herein above regarding the rejection of claims under 35 U.S.C. §102(b) as anticipated by Yeung *et al.* and Kuljis *et al.*, the teachings set forth therein anticipate the claimed subject matter of claim 1 and 29. Further, there is no reason to believe that methods of Snow *et al.* could not be practiced using the transgenic mouse of Yeung *et al.* (*supra*) or Kuljis *et al.* Thus, the methods of claims 7, 10, 12, 13, 15-17, 29 and 41 are enabled by the teachings of Snow *et al.* Therefore, the claims stand rejected as obvious over the teachings of the cited art.

Allowable Subject Matter

Claims 18, 19 and 22 are allowed. The closest art, exemplified by Kobayashi *et al.* (*Id.*) teaches a method comprising providing a mammalian cell; administering antichymotrypsin and a compound; and monitoring cell death. However, Kobayashi *et al.* does not contemplate monitoring phosphorylation of proteins. Although it is known in the art that hyperphosphorylation of proteins such as tau occurs in Alzheimer's disease (see, e.g., Snow *et al.* (*Id.*), page 90), the art does not provide motivation to modify the method of Kobayashi *et al.* to substitute measurement of protein phosphorylation for the cell viability assay disclosed by Kobayashi *et al.*

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

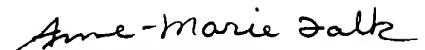
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms


ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER